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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/581,068

**Applicant(s)**

BIGAUD ET AL.

**Examiner**

Stephen Kapushoc

**Art Unit**

1634

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 10 November 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-10 and 13-15 is/are pending in the application.
- 4a) Of the above claim(s) 3-5, 7, 8, 13 and 14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 6, 9, 10 and 15 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB08)
- Paper No(s)/Mail Date 05/31/06; 02/01/08
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ ~~Notice of Informal Patent Application~~
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Claims 1-10 and 13-15 are pending.

Claims 11 and 12 are cancelled.

Claims 3-5, 7, 8, 13 and 14 are withdrawn from examination as detailed below.

Claims 1, 2, 6, 9, 10 and 15 are examined on the merits.

### ***Election/Restrictions***

1. Applicant's election with traverse of the invention of Group 1 (i.e. claims drawn to methods for monitoring transplant rejection comprising analysis of mRNA) and the particular combination of genes consisting of AIF-1 (allograft inflammatory factor -1) in the reply filed on 11/10/2008 is acknowledged. The traversal is on the ground(s) that The special technical feature is the monitoring of rejection using the genes of Tables 1, 2, and 3 (where the particular gene AIF-1 is consonant with Applicant's election). This is not found persuasive because, as detailed in the art rejections in this Office Action, the increased expression of AIF-1 in rejection tissues was in fact known in the prior art. Further, the Examiner maintains that the claims as written drawn to the analysis of either mRNA or protein in the alternative lack unity of invention also because the different analytes (i.e. mRNA or protein) do not in fact share a common structure nor are they both part of the same class of chemical compounds.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 3, 4, 5, 7, 8, 13, 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention (i.e. claims drawn to different inventions (claims 3, 4, 5, 7, 8) or requiring non-elected combinations of genes

(claims 13 and 14), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/10/2008.

### ***Claim Objections***

3. Claims 1 and 2 are objected to over the recitation of non-elected subject matter. The claims recite methods requiring analysis of 'the level of mRNA expression corresponding to or protein encoded by', where such alternative recitation is not consonant with the Election of the invention requiring mRNA analysis. Further it is noted that the alternative requirement of mRNA or protein analysis in a single claim does not satisfy Markush practice for PCT unity of invention because the alternative elements do not have a common structure nor are they part of the same recognized class of compounds.

Claims 1 and 2 are objected to over the recitation of non-elected subject matter. The claims recite methods requiring analysis of 'at least one gene' that is 'as defined in Table 1, 2, or 3', where such alternative recitation is not consonant with the Election of the invention requiring specifically AIF-1 mRNA analysis.

It is noted that no claim is found allowable in this Office Action. Prior to the allowance of any claim, subject matter that is not rejoined with the elected subject matter will be required to be removed from the claims.

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 101 Non-Statutory Subject Matter***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims , 2, 6, 9, 10, and 15 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The rejected claims are drawn to methods of monitoring transplant rejection. The claimed invention falls within an enumerated statutory category, namely a process.

The rejected claims are drawn to methods of monitoring comprising (consonant with the Election) steps of taking baseline expression mRNA expression values and detecting mRNA expression and comparing the expression levels.

In re Bilski No. 2007-1130 (Fed Cir. October 30, 2008) characterizes its machine-transformation test as "the governing test for determining patent eligibility of a process under section 101." Under this test, a process claim is patent-eligible if (and, as applied in Bilski, only if): "(1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." The claims are not directed to patent-eligible subject matter since they are not tied to any particular machine or apparatus and they do not require any particular article to be transformed into another state or thing.

The rejected claim does not require the transformation of an article or physical object to a different state. For example, relevant to the rejected claims, one could take baseline values from a tissue sample by consulting a digital record of gene expression data from an on-line database, and detect mRNA level from a patient sample by consulting data regarding individual expression levels contained in a digital record.

Further one could compare expression levels *in silico* using a computer-run algorithm. Additionally, there is no result tied to the physical world. There is no required transformation of an article or physical object to a different state. Transformation of data is not considered a physical transformation.

As clearly noted in *In re Comiskey No. 2006-1286* (Fed. Cir. Sept. 20, 2007), "the Supreme Court has reviewed process patents reciting algorithms or abstract concepts in claims directed to industrial processes. In that context, the Supreme Court has held that a claim reciting an algorithm or abstract idea can state statutory subject matter only if, as employed in the process, it is embodied in, operates on, transforms, or otherwise involves another class of statutory subject matter, i.e., a machine, manufacture, or composition of matter. 35 U.S.C. § 101." Regarding *In re Comiskey*, the USPTO noted, "[t]he Supreme Court has recognized only two instances in which such a method may qualify as a section 101 process: when the process 'either [1] was tied to a particular apparatus or [2] operated to change materials to a 'different state or thing.'"" (quoting *Flook*, 2006-1286 17 437 U.S. at 588 n.9). In *Diehr*, the Supreme Court confirmed that a process claim reciting an algorithm could state statutory subject matter if it: (1) is tied to a machine or (2) creates or involves a composition of matter or manufacture. 450 U.S. at 184. There, in the context of a process claim for curing rubber that recited an algorithm, the Court concluded that "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Id.* (quoting *Benson*, 409 U.S. at 70);<sup>13</sup> see also *In re*

Schrader, 22 F.3d 290, 295 (Fed. Cir. 1994) (holding when a claim does not invoke a machine, "§ 101 requires some kind of transformation or reduction of subject matter").

Finally, the Comisky opinion states that mental processes- or processes of human thinking- standing alone are not patentable even if they have practical application. The Supreme Court has stated that "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." Benson, 409 U.S. at 67. In Flook the patentee argued that his claims did not seek to patent an abstract idea (an algorithm) because they were limited to a practical application of that idea-updating "alarm limits" for catalytic chemical conversion of hydrocarbons. 437 U.S. at 586, 589-90. The Court rejected the notion that mere recitation of a practical application of an abstract idea makes it patentable, concluding that "[a] competent draftsman could attach some form of post-solution activity to almost any mathematical formula." *Id.* at 590.

In the case of the instantly rejected claims, there is no recitation of producing a real-world result that is tied to a machine or apparatus or causes a transformation of an article. In other words, the outcomes of the rejected methods lack a tie to the machine or apparatus and lack a physical transformation. Thus the claim is rejected as encompassing non-statutory subject matter.

The claims may be made to encompass statutory subject matter if amended to clearly require obtaining a biological sample and detecting analyte levels in the sample,

for example (relevant to the subject matter of independent claim 1 and consonant with the election):

A method of detecting transplant rejection in a test subject, said method comprising:  
a) obtaining a first biological sample from a control subject, said sample comprising nucleic acids, wherein said control subject has a transplanted tissue that is not rejected;  
b) measuring the abundance of AIF-1 (allograft inflammatory factor -1) mRNA in the nucleic acids in said first biological sample;  
c) obtaining a second biological sample from a test subject, said sample comprising nucleic acids, wherein said test subject has a transplanted tissue;  
b) measuring the abundance of AIF-1 mRNA in the nucleic acids in said second biological sample;  
d) comparing the abundance of AIF-1 mRNA in the nucleic acids in said first biological sample to the abundance of AIF-1 mRNA in the nucleic acids in said second biological sample; and  
e) correlating the presence of a statistically significantly greater abundance of AIF-1 mRNA in the nucleic acids in said second biological sample, as compared to the abundance of AIF-1 mRNA in the nucleic acids in said first biological sample, with a transplant rejection in the test subject;  
wherein the first and second biological samples are of the same tissue type.

***Claim Rejections - 35 USC § 112 2<sup>nd</sup> ¶ - Indefiniteness***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 2, 6, 9, 10, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 6, 9, 10, and 15 are unclear over the recitation of the phrase 'the second value' in part c) of each of claims 1 and 2. There is no antecedent basis for any 'second value' in the claims.

Claims 1, 2, 6, 9, 10, and 15 are unclear over the recitation of the phrase 'the gene is as defined in Table 1, 2, or 3' in part c) of each of claims 1 and 2. As consonant with the Election of the particular gene AIF-1, it is noted that Table 1 recites several



elements regarding Table 1, including 'GenBank/RefSeq Identifier', 'Affymetrix probe set' identifiers', and 'fold change' data. It is unclear what particular pieces of information are required to 'define' the gene for the claimed method. The claims may be made more clear by reciting the name of the Elected gene. Further it is noted that MPEP 2173.05(s) indicates that:

Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience."

### ***Claim Rejections - 35 USC § 102***

In the rejection of claims in view of the teachings of the prior art, it is noted that while the claims are very broad with regard to several elements of the claims (e.g.: the claims encompass analysis of any subject organism and rejected tissue type) the specification provides only the example of analysis of kidney tissue in the analysis of kidney transplant rejection in cynomolgus monkey. With regard to the elected invention (i.e. analysis of AIF-1 mRNA in the analysis of tissue rejection), the prior art is replete with examples of the analysis of this analyte with regard to tissue rejection. Thus while the breadth of the claims might be rejected with a scope of enablement rejection under 35 USC 112 1<sup>st</sup> ¶ for the claimed methods requiring a differently elected combination of genes, in the case of the instantly Elected invention, the scope of the claims may be enabled by the teachings of the prior art if not by the teachings of the instant specification.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 9, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Stegall et al (2002).

Stegall et al teaches the analysis of gene expression during rejection of heart allografts as compared to non rejected isografts and non-transplanted tissues.

Relevant to rejected claim 1, Stegall et al teaches baseline levels of AIF-1 mRNA expression in tissue from transplanted subjects known not to develop rejection (Fig 2, AIF, Isograft) (claim 1 step a) and also detecting a level of AIF-1 mRNA expression in the same tissue type in a post-transplant patient (Fig 2, AIF, Allograft) (claim 1 step b), where the graph of the expression levels is a comparison that indicates an increased AIF-1 mRNA expression level predicts an increased risk of developing rejection (p.920 - Transcripts most increased during acute allograft rejection) (claim 1 step c).

Relevant to claims 9 and 10, Stegall et al teaches the analysis of gene expression using RT-PCR (p.915 – Gene expression by RT-PCR) (claim 9) and detecting the level of gene expression of a set of genes (p.914 – RNA isolation and microarray analysis; Tables 2 and 3) (claim 10).

### ***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stegall et al (2002).

Stegall et al teaches the analysis of gene expression during rejection of heart allografts as compared to non rejected isografts and non-transplanted tissues.

Relevant to rejected claim 2, Stegall et al teaches levels of AIF-1 mRNA expression in tissue from transplanted subjects known not to develop rejection (Fig 2, AIF, Isograft) as well as non-transplanted controls (Fig 2, AIF, Normal), (relevant to claim 2 step a) and also detecting a level of AIF-1 mRNA expression in the same tissue type in a post-transplant patient (Fig 2, AIF, Allograft) (relevant to claim 2 step b), and

various numbers of days post-transplantations. The graph of the expression levels (Fig 2) is a comparison that indicates an increased AIF-1 mRNA expression level predicts an increased risk of developing rejection (p.920 - Transcripts most increased during acute allograft rejection) (relevant to claim 2 step c).

Stegall et al does not specifically teach a comparison of gene expression in a tissue obtained from a donor at the day of transplantation and gene expression in a tissue sample from a post-transplantation patient.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have compared gene expression in a tissue obtained from a donor at the day of transplantation and gene expression in a tissue sample from a post-transplantation patient. One would have been motivated to perform such a comparison based on the teaching of Stegall et al that AIF mRNA expression in a normal (non-transplanted control) tissue is significantly lower than AIF expression in rejecting transplant tissue; where such a comparative method would provide an alternative method for the analysis of rejection in a transplanted tissue. There would be a reasonable expectation of success in the methods as the skilled artisan would recognize that the normal control of Stegall et al would be expected to have gene expression similar to a donor tissue prior to transplantation on the day of transplantation.

13. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stegall et al (2002) in view of Chandraker et al 1999.

Stegall et al teaches the analysis of gene expression during rejection of heart allografts as compared to non rejected isografts and non-transplanted tissues. As detailed earlier in this Office Action, Stegall et al teaches baseline levels of AIF-1 mRNA expression in tissue from transplanted subjects known not to develop rejection and also detecting a level of AIF-1 mRNA expression in the same tissue type in a post-transplant patient, where the graph of the expression levels is a comparison that indicates an increased AIF-1 mRNA expression level predicts an increased risk of developing rejection. Thus Stegall et al teaches all of the limitations of independent claim 1, from which rejected claim 6 depends.

Stegall et al does not specifically provide for the analysis of a transplanted subject that is a kidney transplanted subject.

However, the increased expression of AIF-1 in tissues from kidney transplant subjects with rejection was well known in the art at the time the invention was made.

Chandraker et al teaches that significantly higher levels of AIF-1 mRNA were found in a renal transplant with clinical rejection (printed page 4, line 10-11).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have performed an analysis of AIF-1 gene expression according to Stegall et al for the analysis of rejection in a kidney transplant subject. One would have been motivated to do so based on the teachings of Chandraker et al that AIF-1 mRNA is overexpressed in renal transplant rejection, where the skilled artisan would recognize that the methods of Stegall et al would provide for methodological steps for the analysis of renal transplant rejection.

14. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stegall et al (2002) in view of Kelemen et al (2003).

Stegall et al teaches the analysis of gene expression during rejection of heart allografts as compared to non rejected isografts and non-transplanted tissues. As detailed earlier in this Office Action, Stegall et al teaches baseline levels of AIF-1 mRNA expression in tissue from transplanted subjects known not to develop rejection and also detecting a level of AIF-1 mRNA expression in the same tissue type in a post-transplant patient, where the graph of the expression levels is a comparison that indicates an increased AIF-1 mRNA expression level predicts an increased risk of developing rejection. Thus Stegall et al teaches all of the limitations of independent claim 1, from which rejected claim 15 depends.

Stegall et al does not specifically provide for the analysis of a tissue sample that is a body fluid.

However, the analysis of expression of AIF-1 in samples sources comprised in body fluids was known in the art at the time the invention was made.

Kelemen et al teaches the analysis of AIF-1 gene expression in T-lymphocytes and the role of expression in allograft rejection.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have performed the analysis of rejection comprising measuring AIF-1 expression, as taught by Stegall et al, using a body fluid comprising T-lymphocytes, as taught by Kelemen et al. The skilled artisan would have recognized

that such an analysis would provide for alternative methods for rejection analysis, where such methods may not require cardiac biopsy and thus be simpler to perform. One would have had a reasonable expectation of success because Kelemen et al teaches that expression of AIF-1 in T-lymphocytes is related to graft tissue rejection.

### ***Conclusion***

15. No claim is allowed. No claim is free of the teachings of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/  
Art Unit 1634